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Comparative assessment of mortality risk factors between admission and follow-up models among patients hospitalized with COVID-19

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ABSTRACT

Objectives: This study aimed to compare differences in mortality risk factors between admission and follow-up incorporated models.
Methods: A retrospective cohort study of 524 patients with confirmed COVID-19 infection admitted to a tertiary medical center in São Paulo, Brazil from 13 March to 30 April 2020. Data were collected on admission, and the third, eighth and fourteenth days of hospitalization. The hazard ratio (HR) was calculated and 28-day in-hospital mortality risk factors were compared between admission and follow-up models using a time-dependent Cox regression model.
Results: Of 524 patients, 50.4% needed mechanical ventilation. The 28-day mortality rate was 32.8%. Compared with follow-up, admission models under-estimated the mortality HR for peripheral oxygen saturation <92% (1.21 versus 2.09), heart rate >100 bpm (1.19 versus 2.04), respiratory rate >24/min (1.01 versus 1.82) and mechanical ventilation (1.92 versus 12.93). Low oxygen saturation, higher oxygen support and more biomarkers–including lactate dehydrogenase, C-reactive protein, neutrophil-lymphocyte ratio, and urea remained associated with mortality after adjustment for clinical factors at follow-up compared with only urea and oxygen support at admission.
Conclusions: The inclusion of follow-up measurements changed mortality hazards of clinical signs and biomarkers. Low oxygen saturation, higher oxygen support, lactate dehydrogenase, C-reactive protein, neutrophil-lymphocyte ratio, and urea could help with prognosis of patients during follow-up.

Introduction

The SARS-CoV-2 virus has infected more than 100 million and killed nearly 2.5 million people worldwide over the past few months (JHU, 2020). Although most patients are asymptomatic or have mild symptoms, 10% of them require hospitalization and 5% advanced medical support (Wu and McGoogan, 2020). Early identification of severe cases that will demand longer hospitalizations and increased costs can help guide medical decisions and

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manage hospital resources, especially in economically deprived areas.

Clinical risk factors associated with disease progression and death (Center for Diseases Control, 2020; Giannouchos et al., 2020; Tian et al., 2020; Wang et al., 2020) identified in observational studies include older age, hypertension, diabetes, cardiovascular disease, pulmonary disease, chronic renal disease, and cancer. Although there is conflicting evidence about the relative risk of some (e.g., hypertension (Tadic et al., 2020)), a lack of morbidities seems to be protective. Male gender (Boulle et al., 2020; Palaiodimos et al., 2020) and non-white ethnicity (Sze et al., 2020) have also been associated with mortality in some studies.

Among patients hospitalized with COVID-19, several biomarkers have been associated with poor outcomes (Malik et al., 2020; Rod et al., 2020). Non-survivors have been shown to have lower lymphocyte counts and higher levels of D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), and interleukin-6 on admission compared with discharged patients. However, few studies have taken into consideration subsequent (from admission) biomarker levels (Berzuini et al., 2020; Ye et al., 2020) and consequently there is limited validity of their prognostic ability for follow-up reassessments during a hospital stay. In addition, few biomarkers remain associated after adjustment for clinical factors.

Although >20 million people have been infected by COVID-19 in Latin America (JHU, 2020), clinical information on patients' characteristics and outcomes in this region are lacking. This study aimed to: (i) describe the profile of patients admitted with COVID-19 infection to the largest tertiary publicly-funded hospital in Brazil during the first two months of the coronavirus pandemic; and (ii) compare the predictive performance and measures of association between a model with only admission variables and another with the inclusion of repeated measurements throughout hospitalization.

Methods

Study design and population

A retrospective cohort study was carried out on consecutive patients diagnosed with SARS-CoV-2 infection admitted to Hospital das Clínicas, a University of São Paulo affiliated institution, from 13 March to 30 April 2020. SARS-CoV-2 infection was confirmed after a positive real-time quantitative reverse transcription polymerase chain reaction (RT-qPCR) test on a nasopharyngeal or tracheal swab test. During the aforementioned period, Hospital das Clínicas was included in the regional COVID-19 plan to receive only highly suspected or confirmed cases in need of advanced care support (e.g. renal replacement therapy) unavailable at the origin. An assessment algorithm that included the Sequential Organ Failure Assessment (SOFA) and expected long-term survival was used for prioritization of beds. The institutional protocol recommended antibiotics (if pneumonia) and prophylactic anticoagulation; hydroxychloroquine and corticosteroids were optional. Patients with $\leq$24 h of hospitalization, admission diagnoses other than COVID-19, and aged <18 years were excluded. Only the first admission was considered in cases in which more than one was observed. The final cohort included 524 admissions. The project was approved by the National Ethics Committee under research protocol no. 31090720.0.0000.0068.

Clinical variables

All clinical information on demographics, medical morbidities and clinical follow-up were retrieved from electronic health records through a standardized form. The following variables were collected from admission: symptoms, time from symptom onset, vital signs, oxygen support, and laboratory exams. Oxygen support was categorized into four groups reflecting different levels of oxygen dependency: room air, nasal catheter, intermediate oxygen support (Venturi mask, non-rebreather masks, BiPAP and high-flow nasal cannula), and mechanical ventilation. Previously known comorbidities and regular medications were manually retrieved throughout hospitalization. A diagnosis of obesity was retrieved from medical notes because data on weight and height were mostly missing. To analyze the effects of clinical follow-up on mortality, vital signs, laboratory exams and current oxygen support on the third, eighth and fourteenth days of hospitalization were also collected; these days were chosen to reflect both a short and long period of follow-up from admission. Vital signs collection was standardized to the first measurement after 06:00, except for temperature, which was the highest measure of the day.

Medication

Daily medical prescriptions were collected in the first 14 days following admission and re-classified into major groups when more than one single agent was prescribed (e.g. intravenous corticosteroids). To examine the rates of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) dosage prescriptions, the prescribed dosage was divided into three groups during data collection: prophylactic (subcutaneous UFC $\leq$ 15.000 IU/day or subcutaneous LMWH $\leq$ 40 mg/day); optimized (subcutaneous UFC > 15.000 or subcutaneous LMWH > 40 mg/day and <2 mg/kg/day) and anticoagulation (intravenous UFC or subcutaneous LMWH $\geq$ 2 mg/kg/day).

Outcomes

The primary outcome was 28-day mortality. Patients still hospitalized at 28 days were considered alive. Secondary outcomes included overall mortality, thrombotic complications (stroke, myocardial infarction, deep vein thrombosis, and pulmonary thromboembolism) and need for renal replacement therapy.

Statistical analysis

Categorical variables were described with the absolute number and respective percentage, and continuous variables with the median, mean, standard deviation (SD) or interquartile range (IQR), according to variable distribution. Kaplan-Meier survival curves with the inverse probability weights failure function were used to describe the occurrence of deaths on the 28th day of hospitalization (dependent variable). The covariates to be tested (independent variables) were selected based on prior knowledge and vital signs were categorized (e.g. temperature $\geq$37.8 °C) to account for possible non-linear associations. Ethnicity was categorized as white and non-white, due to the small number of sub-groups within the non-white category. To analyze the effects of follow-up variables on mortality, two models were created: one solely based on admission variables, and another with the inclusion of repeated measurements of clinical vital signs and laboratory exams during hospitalization (days 3, 8 and 14). To model the latter, a time-dependent-covariates Cox model was used (Therneau et al., 2020), in which a new time interval was created after a new measurement was added, and an event (death) could happen at every end of an interval. Following this approach, a given subject could have multiple observations but would not have overlapping intervals, and consequently the model was spared from within-subject correlation. Medication prescription and outcomes were not measured because, for most medications studied, there are already ongoing clinical trials (state-of-art for

causal inference) that will ultimately clarify their role in COVID-19 treatment.

Univariable Cox regressions were run for each covariate against the outcome for both admission and time-dependent variables. All covariates with a p-value ≤0.20 were included in a multivariable model for confounding adjustment following a hierarchical framework approach from distal (age, ethinicity and sex) to proximal (vital signs and laboratoray exams) determinants. If after the inclusion the variable maintained $p \leq 0.20$, it was kept in the model; otherwise, it was discarded from subsequent models. Exceptions included age, sex and ethnicity that were included in all models, and vital signs that were tested in the multivariable model regardless of the univariable statistical value. A baseline model with age, sex, ethnicity, and comorbidities was first created, and then two subsequent models (admission and follow-up) were built upon it. The final models are shown in the article and all intermediate ones are in the supplementary material. Cox proportional hazard assumption was evaluated using Schoenfeld residuals and model performance with Harrell's c-statistic.

Few missing values were found (<5%) for most clinical variables except previous medication and laboratory exams (Supplementary Tables 1 and 2). A complete-case analysis was used in the article but a sensitivity analysis with imputation was provided in the supplementary material. Multiple imputations with chained equations (MICE) were performed and Rubin's rules were used (Rubin, 2004) to combine results over 10 imputed datasets. Because of the repeated measurements, imputation followed a multi-level procedure with the participant identification as a cluster for mixed effects. Discrepancies between complete-case and imputation analysis were reported throughout the paper. The alpha was set at 5% (two-tailed). Statistical analysis was performed in R version 3.6.2 (R Core Team 2013) using the MICE (Buuren and Groothuis-Oudshoom, 2010) and survival package (Therneau, 2020).

Results

Patients characteristics and outcomes

Table 1 describes patients' characteristics at admission and their hospitalization outcomes. Of 524 patients, the mean age was 58.7 years (SD 16.4) and most were male (57.44%) with white skin color (68.46%); 131 (25.79%) had smoking exposure. The most common comorbidity was hypertension (59.25%) followed by diabetes (38.58%) and obesity (24.8%). Over one-third of the patients were taking angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) before admission. Many patients had active cancer (13.78%) or previous solid organ transplant (3.94%). The median time from symptom onset to admission was 7 days. Patients had high respiratory rates and low peripheral oxygen saturation in addition to low lymphocyte counts and high levels of D-dimer, CRP and LDH on admission.

Over 24% of the patients were admitted already on mechanical ventilation, and nearly half of them were intubated during hospitalization. The median (IQR) duration of mechanical ventilation was 10 (5–18) days. Nearly 60% (333) were transferred to intensive care units (ICU) and 50% of them died. Thrombotic events were observed in 9.7% of the patients and common complications included deep vein thrombosis (4.21%) and pulmonary thromboembolism (3.05%). The median (IQR) length of hospitalization was 12 (6–21) days. The 28-day in-hospital mortality rate was 32.82%, and 36.92% died during hospitalization. Figure 1 shows the survival probability Kaplan-Meyer curve.

Table 1
Patients characteristics at admission and outcomes.

	N = 524
Age, Mean (SD)	58.72 (16.41)
Sex	
Female	223 (42.56%)
Male	301 (57.44%)
Ethinicity	
White	343 (68.46%)
Black	39 (7.78%)
Mixed	115 (22.95%)
Asian	4 (0.8%)
Life habits	
Non-smoker	377 (74.21%)
Active or previous smoker	131 (25.79%)
Comorbidities	
Hypertension	301 (59.25%)
Diabetes	196 (38.58%)
Obesity	126 (24.8%)
Active cancer	70 (13.78%)
Congestive heart failure	58 (11.42%)
Chronic kidney disease	52 (10.24%)
Atherosclerotic disease	52 (10.24%)
Asthma	22 (4.33%)
COPD	20 (3.94%)
Previous transplant	20 (3.94%)
Dyalisis	13 (2.56%)
Connective tissue disease	9 (1.77%)
Cirrhosis	5 (0.98%)
Medications	
ACE or ARB	137 (37.23%)
Days of symptoms, Median (IQR)	7 (4–9)
Vital signs	
Systolic pressure, Mean (SD)	125.22 (21.8)
Diastolic pressure, Mean (SD)	75.94 (13.1)
Respiratory frequency, Mean (SD)	25.38 (7.06)
Oxygen saturation, Mean (SD)	92.56 (6.42)
Heart rate, Mean (SD)	90.53 (16.68)
Temperature, Mean (SD)	36.49 (0.99)
Oxygen supplementation	
Room air	143 (27.71%)
Nasal catheter	173 (33.53%)
Intermediate oxygen support	75 (14.53%)
Mechanical ventilation	125 (24.22%)
Need for vasoactive drugs	82 (15.95%)
Laboratory exams	
Creatinine (mg/dL), Median (IQR)	0.97 (0.74–1.6)
Urea (mg/dL), Median (IQR)	39 (26–64)
Leucocytes (*1000/mm^3), Median (IQR)	7.56 (5.41–10.59)
Lymphocytes (*1000/mm^3), Median (IQR)	0.9 (0.6–1.3)
Platelets (*1000/mm^3), Median (IQR)	196 (151–261)
D-dimer (ng/dL), Median (IQR)	1345 (692.25–3,181.75)
C-reactive protein (mg/L), Median (IQR)	148.25 (77.83–249.5)
Lactic dehydrogenase (U/L), Median (IQR)	403.5 (309–546)
Hospitalization Days, Median (IQR)	12 (6–21)
Mortality	
In-hospital mortality	192 (36.92%)
28-day in-hospital mortality	172 (32.82%)
ICU admission	333 (63.92%)
ICU mortality	169 (50.75%)
Mechanical ventilation	263 (50.38%)
Days of MV, Median (IQR)	10 (5–18)
Renal replacement therapy	101 (19.31%)
Thromboembolic events	48 (9.16%)
Stroke	2 (0.38%)
Pulmonary thromboembolism	16 (3.05%)
Deep vein thrombosis	22 (4.21%)
Myocardial infarction	10 (1.92%)

ICU = intensive care unit; COPD = chronic obstructive pulmonary disease.

Medication prescriptions

Table 2 shows the prescribed medications and their length of prescription during the first 14 days after admission. Over 80% of the patients received ceftriaxone and azithromycin, and more than 65% oseltamivir as antibiotics. The majority of patients (≥50%)

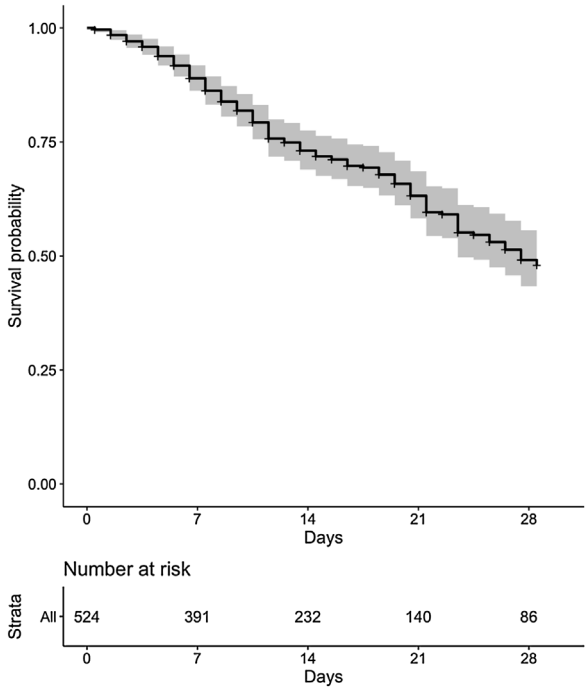

Figure 1. Kaplan–Meyer survival curve for 28-day in-hospital mortality.

received regular prophylactic dosage of LMWH or UFH, and nearly 30% received either an optimized or anticoagulant dosage of LMWH. Few patients (<5%) received hydroxychloroquine or ivermectin. Intravenous corticosteroids were administered to 44%. A high proportion of patients (44.3%) were prescribed neuromuscular blockade and, of those, half for more than four days. Norepinephrine was prescribed for 43% of the patients and opioids in nearly two-thirds of them.

Baseline comorbidities model

Table 3 shows both the univariable and final multivariable models for baseline comorbidities and 28-day in-hospital mortality. It was found that age, chronic kidney disease, cancer, stroke, chronic obstructive disease (COPD), and previous solid organ transplant were associated with increased risk of mortality in the final multivariable model. Conversely, obesity was found to be protective. Both coronary artery disease and congestive heart failure were no longer associated after adjustment, and sensitivity analysis showed similar results after imputation (Supplementary Table 3).

Admission and time-dependent models

Table 4 shows the univariable and multivariable models for admission and follow-up (time-dependent) covariates. The univariable models show hazards under-estimation at admission compared with follow-up (time-dependent) for respiratory rate >24/minute (1.01 versus 1.82), heart rate >100 bpm (1.19 versus 2.04), mean arterial pressure <65 mmHg (2.99 versus 3.53), peripheral oxygen saturation <92% (1.21 versus 2.09), and all levels of oxygen support. Risk factor differences were observed between the admission and follow-up final multivariable models: while only endotracheal intubation and urea levels were associated with increased mortality risk at admission, peripheral oxygen saturation <92%, intermediate oxygen support, mechanical ventilation, CRP, neutrophil-lymphocyte ratio, urea, and LDH were associated with increased risk of death during follow-up. Urea had more hazards (2.25 versus 1.06) on admission compared with follow-up, and mechanical ventilation had less hazards (1.92 versus 4.42). The follow-up model had better performance compared with the admission model (c-statistic 0.829 versus 0.767). None of the final models violated Cox assumptions (global Schoenfeld residuals $p > 0.05$) and sensitivity analysis (Supplementary Tables 4 and 5) with the imputed datasets showed few departures.

Table 2
Medication prescription rates and median (IQR) number of days prescribed during the first 14 days of hospitalization.

Medication	N (%)	Medication	N (%)
Omeprazole	376 (72%)	Nitaxozamide	0 (0%)
Days, Median (IQR)	8 (5–13)	Days, Median (IQR)	0 (0–0)
Ceftriaxone	433 (83%)	Ivermectin	24 (5%)
Days, Median (IQR)	4 (2–6)	Days, Median (IQR)	1 (1–1)
Azithromycin	445 (85%)	LMWH regular	343 (65%)
Days, Median (IQR)	4 (2–5)	Days, Median (IQR)	5 (2–10)
Oseltamivir	341 (65%)	LMWH optimized	111 (21%)
Days, Median (IQR)	2 (1–4)	Days, Median (IQR)	6 (2.5–9)
Other bacterial antibiotic	256 (49%)	LMWH anticoagulant	50 (10%)
Days, Median (IQR)	6 (3–9)	Days, Median (IQR)	6 (2–9)
Corticosteroids IV	233 (44%)	UFH regular	208 (40%)
Days, Median (IQR)	5 (2–9)	Days, Median (IQR)	6 (3–10)
Corticosteroids Oral	103 (20%)	UFH optimized	33 (6%)
Days, Median (IQR)	4 (2–7)	Days, Median (IQR)	7 (3–11)
Hydroxicloroquine	11 (2%)	UFH anticoagulant	29 (6%)
Days, Median (IQR)	2 (1–6)	Days, Median (IQR)	4 (2–6)
Fenoterol	30 (6%)	NSAIDs	10 (2%)
Days, Median (IQR)	4 (1–6.75)	Days, Median (IQR)	1 (1–1.75)
Ipratropium	6 (1%)	Opioids	336 (64%)
Days, Median (IQR)	3 (1.25–4)	Days, Median (IQR)	8 (4–12)
ACEI or ARB	124 (24%)	Neuromuscular blockers	232 (44%)
Days, Median (IQR)	4 (2–8)	Days, Median (IQR)	4 (2–7)
Norepinephrine	230 (44%)	Erytropoietin	12 (2%)
Days, Median (IQR)	6 (3–9)	Days, Median (IQR)	10.5 (5.5–12.25)
Dobutamine	34 (6%)	Furosemide	279 (53%)
Days, Median (IQR)	4 (2–6)	Days, Median (IQR)	5 (2–8)

LMWH = low-molecular-weight heparin; UFH = un-fractioned heparin; NSAIDs = non-steroidal anti-inflammatory drugs; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Table 3
Univariable and multivariable Cox regression models of age, sex, ethnicity, and comorbidities on 28-day in-hospital mortality.

	Univariable		Multivariable	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Age (every 5 years)	1.19	1.13–1.26	1.14	1.10–1.18
Sex				
Female	Reference		Reference	
Male	0.93	0.69–1.25	0.94	0.79–1.14
Ethnicity				
Non-white	Reference		Reference	
White	1.30	0.92–1.83	1.07	0.88–1.32
Past or current smoker	1	0.72–1.41		
Comorbidities				
Obesity	0.61	0.42–0.88	0.79	0.63–0.99
Hypertension	1.33	0.97–1.82		
Diabetes	0.99	0.73–1.34		
Congestive heart failure	1.68	1.10–2.57		
Coronary artery disease	1.53	0.97–2.42		
Chronic kidney disease	1.79	1.22–2.63	1.74	1.36–2.22
Cancer	2.17	1.51–3.12	1.84	1.45–2.34
Stroke	2.97	1.51–5.84	2.34	1.50–3.65
Previous transplant	1.60	0.84–3.04	1.90	1.32–2.75
COPD	2.54	1.44–4.48	1.79	1.26–2.54
Asthma	0.36	0.09–1.46		
Auto-immune disease	1.07	0.34–3.36		
Regular medications				
ACEI or ARB	0.94	0.62–1.42		
Concordance (C-statistic)			0.667	

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Table 4
Comparison of 28-day in-hospital mortality risk factors between admission and follow-up (time-dependent) models.

	Admission				Follow-up (time-dependent)			
	Univariable		Multivariable[a]		Univariable		Multivariable[a]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Symptom days	0.98	0.94–1.02			0.98	0.94–1.02		
Vital signs								
Mean arterial pressure <65 mmHg	2.99	1.53–5.86	1.75	0.64–4.77	3.53	2.25–5.53	1.2	0.66–2.17
Temperature ≥37.8 °C	0.71	0.41–1.26			1.02	0.72–1.44		
Respiratory rate >24/minute	1.01	0.75–1.36			1.82	1.34–2.46	1.18	0.80–1.74
Heart rate >100 bpm	1.19	0.86–1.65			2.04	1.50–2.77	1.51	0.99–2.31
Oxygen saturation <92%	1.21	0.88–1.66	1.38	0.89–2.16	2.09	1.55–2.82	1.79	1.21–2.63
Oxygen support								
Room air	Reference		Reference		Reference		Reference	
Nasal catheter	1.19	0.74–1.92	1.48	0.76–2.90	4.10	1.22–13.74	1.92	0.54–6.87
Intermediate oxygen support	1.66	1.00–2.78	1.57	0.77–3.20	8.56	2.60–28.22	2.76	0.77–9.91
Mechanical ventilation	1.92	1.23–3.00	2.02	1.08–3.79	12.93	4.10–40.77	4.45	1.32–14.97
Laboratory exams								
Creatinine (mg/dL)	1.14	1.08–1.20			1.24	1.17–1.31		
Urea (every 50 mg/dL)	1.64	1.47–1.83	2.25	1.74–2.91	1.54	1.40–1.68	1.06	1.03–1.08
C-reative protein (every 100 mg/dL)	1.19	1.04–1.35			1.47	1.31–1.66	1.18	1.00–1.40
Neutrophil/lymphocyte ratio	1.02	1.01–1.03			1.02	1.01–1.03	1.01	1.00–1.02
D-dimer (every 1000 ng/mL)	1.01	1.00–1.02	0.99	0.98–1.00	1.02	1.01–1.03		
Platelets (every 100,000/mm^3)	1.08	1.05–1.12			1.09	1.06–1.11	0.88	0.75–1.04
Lactate dehydrogenase (every 100 U/L)	0.92	0.76–1.12			0.76	0.67–0.86	1.06	1.03–1.09
Concordance (c-statistic)			0.767				0.829	

[a] Adjusted for age, sex, ethinicity, comorbidities and obesity.

Discussion

This study described the case fatality rate and clinical correlates of mortality among a cohort of hospitalized patients with severe COVID-19 in the largest tertiary publicly-funded hospital in Brazil during the first two months of the coronavirus pandemic. In addition, it showed that the inclusion of repeated clinical and laboratorial measurements improved the models' predictive performance and changed measures of association (hazard ratio) among correlates.

A higher rate of overall mortality was observed compared with tertiary centers in higher-income countries (Salacup et al., 2020; Gregoriano et al., 2020; Rieg et al., 2020; Halem et al., 2020). This can be partly explained by the higher prevalence of severe disease and need for invasive oxygen supplementation found in this cohort: nearly 50% of the patients needed mechanical ventilation support compared with 12%, 19%, 22%, and 26% of patients in similar centers in Belgium (Halem et al., 2020), Switzerland (Gregoriano et al., 2020), United States (Salacup et al., 2020), and Germany (Rieg et al., 2020), respectively. Considering only those

admitted to ICU, the current mortality rate (50%) was comparable with Germany (47%) (Rieg et al., 2020), lower than Russia (64%) (Moiseev et al., 2020) but higher than New York (22%) (Richardson et al., 2020), Lombardy (26%) (Temel et al., 2020), and Belgium (38%) (Halem et al., 2020). This study also observed a lower rate of venous and arterial thrombosis compared with previous literature (Al-Ani et al., 2020).

Prescription of antibiotics was very common (≥80%) and mostly included a combination of ceftriaxone and azithromycin in addition to oseltamivir. Over 45% of patients also received a second bacterial antibiotic during hospitalization. These rates were higher than similar centers (Gregoriano et al., 2020; Rieg et al., 2020; Halem et al., 2020) and reflected the institutional protocol at that time. On the other hand, prescription of hydroxychloroquine, ivermectin and nitaxozamide was extremely low (<5%), which contrasts with the large proportion of patients who were prescribed hydroxychloroquine in Switzerland (39%) (Gregoriano et al., 2020), Germany (43%) (Rieg et al., 2020), Italy (52%) (Fumagalli et al., 2020), and the United States (60%) (Salacup et al., 2020). At that time, even though there was no evidence of a hydroxychloroquine benefit, it is noteworthy that many institutions worldwide routinely adopted its use during the initial months of the pandemic. The low prescription rate in the current cohort can be explained by the lack of institutional recommendation and the skepticism regarding its use in a university-affiliated hospital. Interestingly, although the benefit of corticosteroids in COVID-19 was not proven at that time (Horby et al., 2020), nearly 45% of the patients received intravenous corticosteroids and of those, at least half for five days or more.

Consistent with previous literature (Rod et al., 2020; Wang et al., 2020) it was found that older age, cancer, previous solid organ transplant, chronic renal disease, COPD, and stroke were associated with increased mortality risk. No association between previous use of ARB or ACE and mortality was observed (Zhang et al., 2020). Commonly reported risk factors for severe disease in general population studies–such as hypertension, diabetes and male gender–might have been underestimated because of the selection bias induced by including only tertiary hospitalized patients. In fact, selection and collider bias can ultimately lead to association distortions (attenuation, inflation or reversal) in observational studies (Griffith et al., 2020) and should prompt cautious interpretation of results. Similar reasoning can be applied to the protective effect of obesity. Although there is considerable evidence about the association of obesity and the higher risk of disease severity in COVID-19 patients (Palaiodimos et al., 2020; Simonnet et al., 2020; Tartof et al., 2020), once the disease progresses the estimated effect direction might change when only a subset of patients is considered (obesity paradox). Similar findings have been observed for coronary artery disease (Gruberg et al., 2002) and acute respiratory distress syndrome (Ni et al., 2017) and may be applicable to COVID-19; however, further studies are needed to answer this question.

Identifying patients at higher risk of death can guide medical decisions and help manage hospital resources, especially in an under-resourced setting. Many prognosis-related factors have been identified for COVID-19; however, most of them rely on admission laboratory and clinical signs (Ou et al., 2020; Wynants et al., 2020), and consequently have limited validity for follow-up daily reassessments. In addition, it is expected that variables collected at admission change their prognostic ability when repeated measurements are included. As an example, this study showed that clinical signs hazards were under-estimated at admission compared with follow-up; this possibly happened because vital signs capture late changes that are ultimately associated with death (Bruera et al., 2014) and are under-represented at admission for most patients who will die much later during the course of disease. For instance, oxygen support (a proxy for respiratory deterioration) nearly doubled the hazards from admission because only 40% of all intubated patients were on mechanical ventilation at admission; similar findings were observed for heart rate, respiratory rate and mean arterial pressure.

Similarly, laboratory tests help risk stratification but are prone to the same bias when only admission data are included. Consistent with prior literature (Malik et al., 2020; Rod et al., 2020), this study showed that most studied biomarkers were associated with mortality when unadjusted for clinical factors. However, because it is expected that clinical tests are ordered after clinical evaluation, it is imperative to consider their significance according to patients' past medical history and clinical signs (adjusted models). In this regard, this study showed that more markers were associated with mortality during follow-up (urea, CRP, neutrophil-lymphocyte ratio, and LDH) compared with admission (urea), and might help physicians with patients' prognosis during follow-up. Of those markers, the neutrophil-lymphocyte ratio had already been shown to have prognostic ability in a similar study with follow-up measurements (Berzuini et al., 2020). Notably, although widely requested on admission (>70%), no role for D-dimer was found in prognostication. Whether it can guide future therapies, such as for anticoagulation, remains a question and no evidence has been found for routine dosage.

Limitations are unavoidable and essential to discuss. First, this study was from a single center and might not reflect the conditions found in private counterparts or primary and secondary settings. Second, the data represent the initial surge of the pandemic subject to the learning curve. Third, chart diagnosis was considered for comorbidities and therefore prone to under-reporting or measurement error (obesity). Fourth, because of test unavailability, there were no data on IL-6 levels, which may have had a role in the prognosis of COVID-19 infected patients. Finally, treatments were heterogeneous and medication prescriptions and outcomes were not addressed.

Strengths of this study included the detailed description of different outcomes and medication prescription rates among hospitalized patients from a tertiary public hospital in Brazil, and the analysis of follow-up measurements and their clinical interpretation for COVID-19 prognosis, which few previous studies have taken into consideration (Berzuini et al., 2020).

In summary, this study described the clinical outcomes and patterns of prescription during the first two months of the COVID-19 pandemic in a tertiary center in Brazil. The incorporation of follow-up measurements, in addition to improving mortality prediction, changed the mortality hazards of vital signs and biomarkers compared with admission. Peripheral oxygen saturation, oxygen support, LDH, urea, C-reactive protein, and neutrophil-lymphocyte ratio, in addition to previously known comorbidities, could help prognose COVID-19 patients at follow-up assessments.

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Conflictsof interest

The authors declare no competing interests.

Availability of data and material

Data are available from the authors upon reasonable request.

Authors contributions

FLN, GAS, ALC, TLB, FVDB, JA, GPL, JCO, FCA, MRAA, AAD, MFDSD, FCBS, and DFD collected the data. FLN, GAS, ALC, and ACFM planned and carried out the analysis. TLB, FVDB, JA, GPL, JCO, FCA, MRAA, AAD, MFDSD, FCBS, and DFD contributed to interpretation of results. FLN and GAS wrote the manuscript with contribution from ALC, TLB, FVDB, and GPL. ACFM and MAM revised the manuscript and supervised the project. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.03.013.

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